

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
5 July 2001 (05.07.2001)

PCT

(10) International Publication Number
WO 01/47451 A1

(51) International Patent Classification⁷: **A61F 13/00**,
2/00, A61K 31/565, A61M 25/10, 29/00, A61P 9/10

(74) Agent: MORAN, Kevin, P.; Michael Best & Friedrich
LLP, 100 East Wisconsin Avenue, Milwaukee, WI 53202
(US).

(21) International Application Number: PCT/US00/35641

(22) International Filing Date:
29 December 2000 (29.12.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/173,451 29 December 1999 (29.12.1999) US

(71) Applicants and

(72) Inventors: NEW, Gishel [AU/US]; 167 East 77th Street,
#18, New York, NY 10021 (US). MOSES, Jeffrey, W.
[US/US]; 1175 Park Avenue, 12A, New York, NY 10021
(US). KIPSHIDZE, Nicholas [GE/US]; 345 East 80th
Street, 25B, New York, NY 10021 (US). ROUBIN, Gary,
S. [AU/US]; 350 East 79th Street, New York, NY 10021
(US). LEON, Martin, B. [US/US]; 875 Park Avenue,
#12B, New York, NY 10021 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,
DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

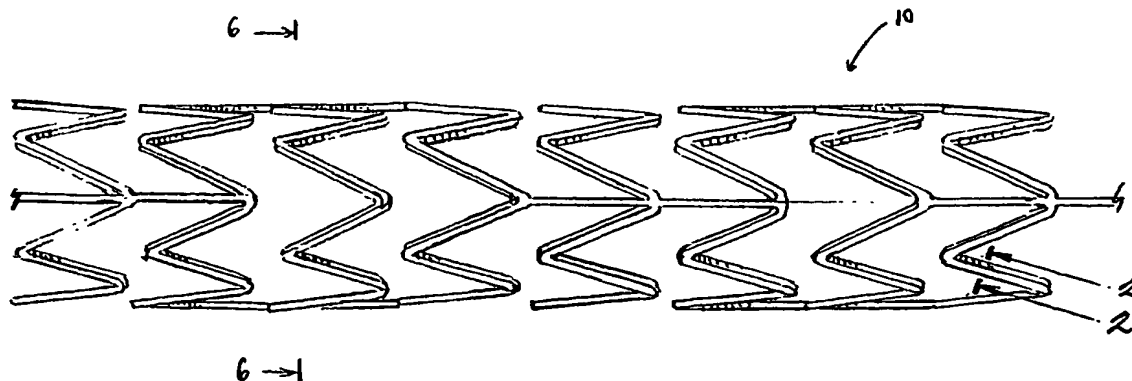
(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— With international search report.

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: APPARATUS AND METHOD FOR DELIVERING COMPOUNDS TO A LIVING ORGANISM



(57) Abstract: A method of treating or preventing vascular disease in a living organism. The method includes delivering an effective amount of a composition including a sex hormone, anti-hormone, sex-hormone agonist, steroid-hormone inhibitor/antagonist (partial or full), selective estrogen receptor modulator (SERM), or a combination thereof, to an affected area of a living organism.

WO 01/47451 A1

APPARATUS AND METHOD FOR DELIVERING COMPOUNDS TO A LIVING ORGANISM

FIELD OF THE INVENTION

5 The invention relates to local-delivery devices and methods for treating and preventing vascular diseases in a living organism. More particularly, the invention relates to local-delivery devices coated with a composition comprising a sex hormone, anti-hormone, sex-hormone agonist, steroid-hormone inhibitor/antagonist (partial or full), selective estrogen receptor modulator (SERM), or a combination thereof. The local-
10 delivery device, e.g. a stent, catheter or balloon-injection catheter, is inserted into an affected area of a living organism to treat or prevent the vascular disease.

BACKGROUND OF THE INVENTION

 Vascular diseases include diseases that affect areas of a living organism relating to
15 or containing blood vessels.

 For example, stenosis is a narrowing or constricting of arterial lumen in a living organism (e.g., a human) usually due to atherosclerosis/coronary heart disease (CHD). Restenosis is a recurrence of stenosis after a percutaneous intervention such as angioplasty and stenting. The underlying mechanisms of restenosis comprise a combination of effects
20 from vessel recoil, negative vascular remodeling, thrombus formation and neointimal hyperplasia. It has been shown that restenosis after balloon angioplasty is mainly due to vessel remodeling and neointimal hyperplasia.

 Treatment for stenosis and restenosis varies. Stenosis caused by CHD often forces individuals to restrict and limit their activity levels in order to avoid complications, stroke,
25 heart attack, sudden death and loss of limb or function of a limb stemming from the stenosis. The reconstruction of blood vessels, arteries and veins may also be needed to treat individuals suffering from stenosis and restenosis. Coronary bypass can also be utilized to revascularize the heart and restore normal blood flow. In other cases, balloon angioplasty may be conducted to increase the orifice size of affected areas. Overall, these
30 treatments address the problems associated with stenosis, but they also create a high rate of restenosis that can result in recurrence of cardiac symptoms and mortality. Moreover, these treatments are not preventative in nature, and therefore generally are not utilized until the patient or individual has already developed stenosis.

One type of stenosis and restenosis is atherosclerosis. Atherosclerosis affects medium and large arteries and is characterized by a patchy, intramural thickening that encroaches on the arterial lumen and, in most severe form, causes obstruction. The atherosclerotic plaque consists of an accumulation of intracellular and extracellular lipids, smooth muscle cells and connective tissue. The earliest lesion of atherosclerosis is the fatty streak that evolves into a fibrous plaque coating the artery. Atherosclerotic vessels have reduced systolic expansion and abnormal wave propagation. Treatment of atherosclerosis is usually directed at its complications, for example, arrhythmia, heart failure, kidney failure, stroke, and peripheral arterial occlusion.

New and improved methods and devices are being sought for treatment and prevention of vascular diseases such as stenosis, restenosis and atherosclerosis.

SUMMARY OF THE INVENTION

The present invention provides a method of treating or preventing vascular disease in a living organism. The method includes applying an effective amount of a composition comprising a sex hormone, anti-hormone, sex-hormone agonist, steroid-hormone inhibitor/antagonist (partial or full), selective estrogen receptor modulator (SERM), or a combination thereof, to a local-delivery device. The method also includes inserting the local-delivery device into an affected area of a living organism and allowing at least a portion of the sex hormone, anti-hormone, sex-hormone agonist, steroid-hormone inhibitor/antagonist (partial or full), selective estrogen receptor modulator (SERM), or combination thereof, to gradually release or inject into the affected area of the living organism.

The invention also provides a local-delivery system effective for treating and preventing vascular disease in a living organism. The system includes a local-delivery device and a composition at least partially applied thereto. The composition comprises a sex hormone, anti-hormone, sex-hormone agonist, steroid-hormone inhibitor/antagonist (partial or full), selective estrogen receptor modulator (SERM), or a combination thereof.

Other features and advantages of the invention will become apparent to those skilled in the art upon review of the following detailed description and claims. Before embodiments of the invention are explained in detail, it is to be understood that the invention is not limited in its application to the details of the composition and concentration of components set forth in the following description. The invention is capable of other embodiments and of being practiced or being carried out in various ways.

Also, it is understood that the phraseology and terminology used herein is for the purpose of description and should not be regarded as limiting.

BRIEF DESCRIPTION OF THE DRAWINGS

5 Figure 1 is a perspective view of a stent embodying the invention.

Figure 2 is a cross-sectional view taken along line 2--2 in Figure 1.

Figure 3 is a perspective view of a balloon-injection catheter embodying the invention.

Figure 4 is cross-sectional view taken along line 4--4 of Figure 3.

10 Figure 5 is a cross-sectional view taken along line 5--5 in Figure 5, wherein the catheter is inserted into an affected area of a living organism.

Figure 6 is a cross-sectional view taken along line 6--6 of Figure 1.

DESCRIPTION OF THE INVENTION

15 The present invention provides apparatuses and methods for delivering a composition to a localized area of a living organism. More particularly, the invention provides apparatuses and methods for locally delivering a sex hormone (e.g. estrogen), an anti-hormone, a sex-hormone agonist, a steroid-hormone inhibitor/antagonist (partial or full) or a selective estrogen receptor modulator (SERM), or a combination thereof, to a
20 portion of a living organism inflicted by or susceptible to a vascular disease such as stenosis or restenosis.

Recent research has uncovered that different sex hormones may have different effects on vascular functions. For example, gender differences in cardiovascular disease have largely been attributed to the protective effects of estrogen in women; premenopausal
25 women have a lower incidence of Coronary Heart Disease. In particular, estrogen has well-known beneficial effects on lipid profile. More importantly, estrogen may directly affect vascular reactivity, which is an important component of atherosclerosis. Recent epidemiological studies suggest that hormone replacement therapy (HRT) may reduce the risk of coronary-artery disease in post-menopausal women. More particularly, many
30 epidemiological studies suggest that estrogen replacement therapy (ERT) may be cardioprotective in postmenopausal women. The beneficial effects of these hormone therapies may also be applicable to males.

The mechanisms for these beneficial effects are probably multifactorial. Estrogen is known to favorably alter the atherogenic lipid profile and may also have a direct action

on blood vessel walls. Estrogen can have both rapid and long-term effects on the vasculature including the local production of coagulation and fibrinolytic factors, antioxidants and the production of other vasoactive molecules, such as nitric oxide and prostaglandins, all of which are known to influence the development of vascular disease.

5 Experimental work suggests that estrogen can also act on the endothelium and smooth muscle cells either directly or via estrogen receptors in both men and women. This appears to have an inhibitory effect on many steps in the atherosclerotic process. With respect to the interventional cardiology, estrogen appears to inhibit the response to balloon injury to the vascular wall. Estrogen can repair and accelerate endothelial cell
10 growth in-vitro and in-vivo. Early restoration of endothelial cell integrity may contribute to the attenuation of the response to injury by increasing the availability of nitric oxide. This in turn can directly inhibit the proliferation of smooth muscle cells. In experimental studies, estrogen has been shown to inhibit the proliferation and migration of smooth muscle cells in response to balloon injury. Estrogen has also proved to inhibit adventitial
15 fibroblast migration which may in turn have an effect on negative remodeling.

Effective Compositions

Sex hormones and sex-hormone agonists may be helpful in preventing and treating certain vascular diseases. Examples of suitable sex hormones include, but are in no way
20 limited to, estrogens, progesterones, testosterone, dehydroepiandrosterones (DHEAs) and dehydroepiandrosteronesulfates (DHEAS). Of these compounds, estrogen has proven to be the most effective in preventing and treating vascular diseases. Naturally occurring/plant estrogens or phytoestrogens including isoflavones such as genistein, daidzein and resveratrol are also useful in the treatment of vascular disease. Suitable sex-
25 hormone agonists include, but are in no way limited to, estradiol, estrone, ethinyl estradiol and conjugated equine estrogens.

In addition, anti-hormones and steroid-hormone inhibitors/antagonist (partial or full) may be effective in preventing vascular diseases. Anti-hormones inhibit or prevent the usual effects of certain other hormones, thereby increasing the relative effectiveness of
30 hormones that are not being inhibited or prevented by these anti-hormones. Anti-hormones effective in preventing vascular diseases include, but are not limited to, anti-estrogens (e.g. Faslodex), anti-androgens (e.g. cyproterone acetate) and anti-testosterone (e.g. anti-testosterone wild-type Fab fragment and mutant Fab fragments). Examples of

steroid-hormone inhibitors/antagonist (partial or full) include, but are not limited to, aminogluthemide, anastrozole and letrozole.

Selective estrogen receptor modulators (SERMS), including but not limited to raloxifene, tamoxifen and idoxifene, may also be effective in treating or preventing
5 vascular diseases such as stenosis and restenosis.

These compounds are generally found in a powdered form. In order to apply the compound to a local-delivery device or to locally inject the compound into an affected area, the powder is generally mixed with a solution of saline or ethanol. This facilitates coating the local-delivery devices or injecting the composition as described below. The
10 composition can also be mixed into another solution, gel or substance to control the rate of release from the stent and into the tissue.

Local-Delivery Systems

Local delivery of the above-listed compositions in the exact area of disease or
15 potential disease avoids the negative systemic effects these compounds can produce when administered generally. For example, oral use of conjugated equine estrogen in combination with a progestin may have effects on the coagulation pathways that attenuate the benefits that may potentially occur to a vascular wall. In addition, hyperplastic effects of estrogen on the uterus and breast tissue may exist when estrogen is administered
20 systemically. Moreover, general administration may result in potential feminizing effects in males.

The local delivery of estrogen and the other compositions described above to atherosclerotic plaque is a promising alternative to the systemic use of this hormone. The basic anti-atherogenic properties of these compositions and their potential to inhibit
25 neointimal proliferation while simultaneously attenuating endothelial repair make them ideal for local administration in the coronary artery to inhibit restenosis. Localized delivery of other compositions comprising sex hormones, anti-hormones, sex-hormone agonists, steroid-hormone inhibitors/antagonist (partial or full) or selective estrogen receptor modulators (SERMS), or combinations thereof, to the vasculature may prevent
30 and treat vascular diseases such as stenosis, restenosis and atherosclerosis.

The local-delivery systems generally comprise a local-delivery device and at least one of the effective compositions described above. The compositions can be delivered locally to tissue, tubular organs, blood vessels, the coronary or peripheral of organs as well

as to muscles (myocardium, skeletal or smooth muscles). The compositions can also be injected directly into the vessel, vessel wall or muscle.

Examples of local-delivery devices include, but are not limited to, stents and catheters. In one embodiment of the invention, the local-delivery system is a stent that delivers the above-described compositions to the localized portion of the body of a living organism. Figure 1 illustrates a stent 10, which is a hollow member that lies within the lumen of a tubular structure and provides support and assures patency of an intact but contracted lumen. Stents may be made from stainless steel or any other suitable material. Effective compositions as described above coat or are applied to the stent. Figure 2 shows a portion of the stent 10 coated with a composition 12 in cross-section. Because the stent remains in the artery after the angioplasty procedure is performed, it enables the composition 12 to slowly diffuse from the outside of its surface 10 into the adjacent atherosclerotic plaque to which it can affect. The rate of this diffusion varies according to the molecular weight of the compound being administered. Also, the structure of the stent and the type of coating applied thereto also affect the rate of diffusion.

In another embodiment, an effective composition is applied to an injection catheter, and more particularly to a balloon-injection catheter 14. As shown in Figs. 3 and 4, a balloon-injection catheter 14 is similar to a balloon angioplasty, except for the added feature of a chamber 16 including injection ports 18 for injecting the compositions described above. Figure 5 illustrates a balloon-injection catheter 14 in cross-section after being injected into an affected area 20 of a living organism. The hormone can be injected directly into the plaque, vessel wall or tissue 22 via these injection ports 18. If an injection catheter injects the compound into the plaque 22, the composition releases immediately after injection. Accordingly, there is no residual release of the composition once the injection catheter is removed.

Angiographic, angioplasty, delivery and infusion catheters may also be used to deliver these compounds to affected areas. Using these devices, the above-described compositions can be locally delivered to a variety of body structures including grafts, saphenos vein grafts, arterial grafts, synthetic grafts, implants, prostheses or endoprotheses, homo or zeno grafts, cardiac muscle, skeletal or smooth muscle body structure.

Applying the Effective Compositions to the Local-Delivery Devices

Application of these effective compositions to a stent or other local-delivery device can be achieved in a number of different ways.

First, the compound can be mechanically or electromechanically bonded to the delivery device, e.g. by a covalent bonding process. When using such a physical application the compounds are directly embedded into a metal or other suitable substance from which the local-delivery system is comprised.

Second, the effective composition can also be applied using a chemical coating/bonding process, whereby layers of a suitable pharmaceutical agent, vehicle, or carrier entrap the compound. In this manner, a biological or pharmacological coating already present on the local-delivery device acts as a platform for coating the compounds described above. Examples of platforms include, but are not limited to, silicon carbide, carbon, diamond or diamond-like coating, e.g. polytetrafluoroethylene, hylauronic acid or polyactone. Other suitable synthetic pharmaceutical agents include, but are not limited to, polyurethane, segmented polyurethane, poly-L-lactic acid, cellulose ester, polyethylene glycol as well as polyphosphate esters. Naturally occurring vehicles or carriers include collagens, laminens, heparins, fibrins, and other naturally occurring substances that absorb to cellulose. Using a chemical coating of the stent or other device is particularly advantageous in that it allows the compound or sex hormone to slowly release from the carrier, vehicle, or agent. This extends the time that the affected portion of the body sustains the efficacious effects of the compounds. The manner in which these carriers or vehicles interact with the device material as well as the inherent structure of these carriers and vehicles provide a diffusion barrier, thereby controlling the release of the entrapped compounds or sex hormones.

Estrogen and the other effective compositions described above can also be coated onto or delivered with other drugs or compounds in order to administer synergistic treatment. Examples of other suitable drugs and compounds include antibodies, oligonucleotides (e.g. antisense oligonucleotides), antiproliferatives, anticancer or antimicrotubular agents (e.g. rapamycin, paclitaxel), antiproliferative agents, growth factors, genes, antisense or antithrombotic agents or any other chemical or biological compound that will act synergistically to increase the effectiveness of the primary hormone or compound. For example, stent coatings can absorb and release these materials, thus providing an inert depot for controlled drug administration. Loading of the

drug can occur for example via diffusion of the drug solution into the coating by hydration/swelling of the polymer matrix.

Example

- 5 In one preferred example, powdered estrogen is mixed with a carrier such as ethanol to form a solution or gel. The estrogen gel is then applied to a stainless steel stent using chemical coating methods that are well-known in the art. Subsequently, the coated stent is inserted into an arterial lumen of a human being suffering from atherosclerosis. In other words, the coated stent is inserted into an artery plagued by patchy, intramural
- 10 plaque. The estrogen in the coating slowly diffuses into and penetrates the plaque, thereby providing treatment for this vascular disease.

CLAIMS

I claim:

- 5 1. A method of treating or preventing vascular disease in a living organism,
the method comprising:
 applying an effective amount of a composition comprising a sex hormone,
anti-hormone, sex-hormone agonist, steroid-hormone inhibitor/antagonist (partial or full),
selective estrogen receptor modulator (SERM), or a combination thereof, to a local-
10 delivery device;
 inserting the local-delivery device into an affected area of a living
organism; and
 allowing at least a portion of the sex hormone, anti-hormone, sex-hormone
agonist, steroid-hormone inhibitor/antagonist (partial or full), selective estrogen receptor
15 modulator (SERM), or combination thereof, to gradually release or be injected into the
affected area of the living organism.
2. The method of claim 1, wherein the local-delivery device is a stent.
- 20 3. The method of claim 1, wherein the local-delivery device is a balloon-
injection catheter.
4. The method of claim 1, wherein the composition comprises a sex hormone
and the sex hormone is estrogen, progesterone, testosterone, dehydroepiandrostrone
25 (DHEA), dehydroepiandrosteronesulfate (DHEA) or a combination thereof.
5. The method of claim 4, wherein the composition comprises a sex hormone
and the sex hormone is estrogen.
- 30 6. The method of claim 1, wherein the composition comprises a sex-hormone
agonist and the sex-hormone agonist is estradiol, estrone, ethinyl estradiol, conjugated
equine estrogen, or a combination thereof.

7. The method of claim 1, wherein the composition comprises an anti-hormone and the anti-hormone is an anti-estrogen, Faslodex, an anti-androgen, cyproterone acetate, an anti-testosterone, or a combination thereof.

5 8. The method of claim 1, wherein the composition comprises a steroid-hormone inhibitor/antagonist (partial or full) and the steroid-hormone inhibitor/antagonist (partial or full) is aminogluthemide, anastrozole, letrozole, or a combination thereof.

9. The method of claim 1, wherein the composition comprises a SERM and
10 the SERM is a raloxifene, tamoxifen, idoxifene, or a combination thereof.

10. The method of claim 1, wherein the affected area of the living organism is tissue, tubular organ, blood vessels, coronary or peripheral of organs, myocardium, skeletal, smooth muscles or a combination thereof.

15 11. The method of claim 1, wherein the composition is applied to the local-delivery device using a chemical coating comprising a suitable pharmaceutical agent, vehicle or carrier.

20 12. The method of claim 1, wherein the composition is applied to the local-delivery device using a mechanical or electromechanical bond.

13. A local-delivery system effective for treating and preventing vascular disease in a living organism comprising:

25 a local-delivery device; and
a composition comprising a sex hormone, anti-hormone, sex-hormone agonist, steroid-hormone inhibitor/antagonist (partial or full), selective estrogen receptor modulator (SERM), or a combination thereof, the composition being applied to the local-delivery device.

30 14. The system of claim 13, wherein the local-delivery device is a stent.

15. The system of claim 13, wherein the catheter is a balloon-injection catheter.

16. The system of claim 13, wherein the composition comprises a sex hormone and the sex hormone is estrogen, progesterone, testosterone, dehydroepiandrostrone (DHEA), dehydroepiandrosteronesulfate (DHEA), or a combination thereof.

5 17. The system of claim 16, wherein the sex hormone is estrogen.

18. The system of claim 13, wherein the composition comprises a sex-hormone agonist and the sex-hormone agonist is estradiol, estrone, ethinyl estradiol, conjugated equine estrogen, or a combination thereof.

10

19. The system of claim 13, wherein the composition comprises an anti-hormone and the anti-hormone is an anti-estrogen, Faslodex, an anti-androgen, cyproterone acetate, an anti-testosterone, or a combination thereof.

15 20. The system of claim 13, wherein the composition comprises a steroid-hormone inhibitor/antagonist (partial or full) and the steroid-hormone inhibitor/antagonist (partial or full) is aminoglutethimide, anastrozole, letrozole, or a combination thereof.

20 21. The system of claim 13, wherein the composition comprises a SERM and the SERM is raloxifene, tamoxifen, idoxifene, or a combination thereof.

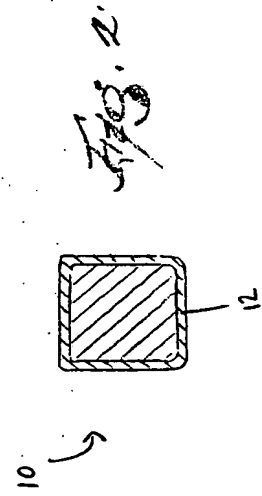
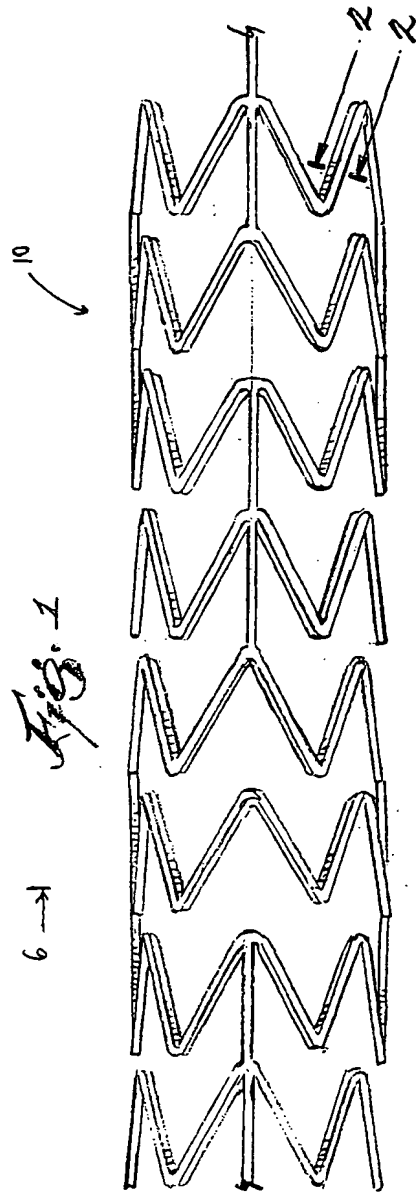
22. The system of claim 13, wherein the affected area of the living organism is tissue, tubular organ, blood vessels, coronary or peripheral of organs, myocardium, skeletal, smooth muscles or combinations thereof.

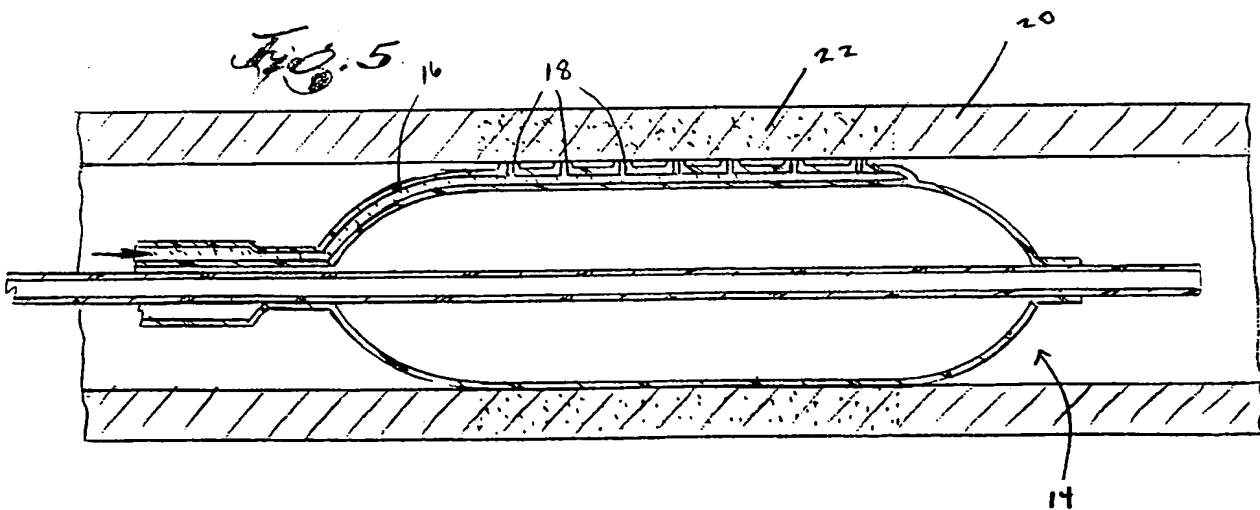
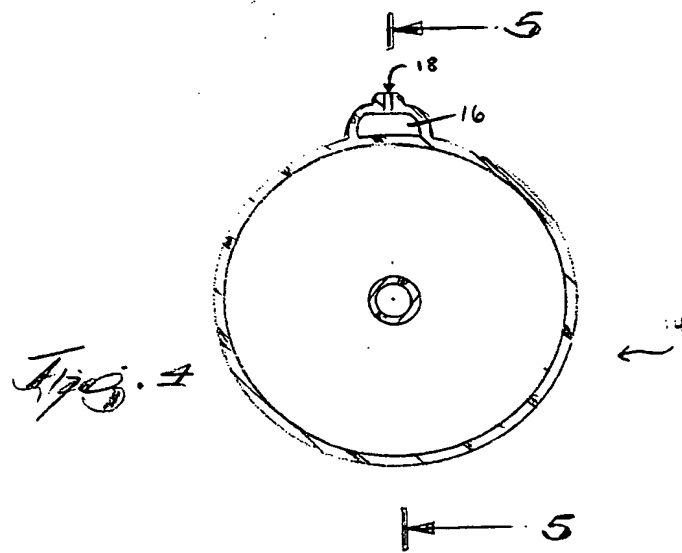
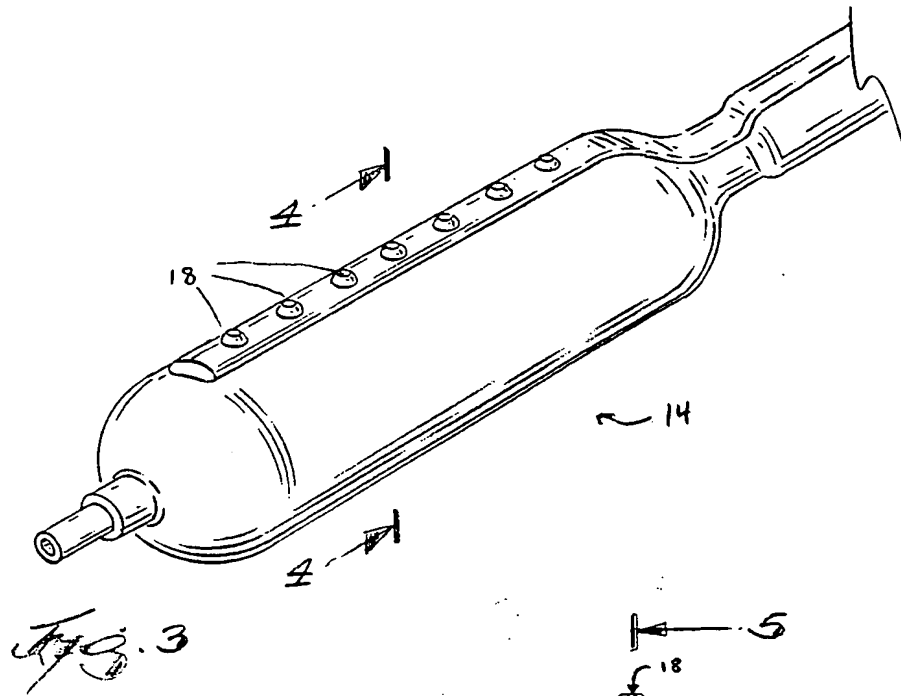
25

23. The system of claim 13 further comprising a compound synergistically increasing the effectiveness of the composition, the compound being applied to the local-delivery device.

30 24. The system of claim 13, wherein the composition is applied to the local-delivery device using a chemical coating.

25. The system of claim 13, wherein the composition is applied to the local-delivery device using a mechanical or electromechanical bond.





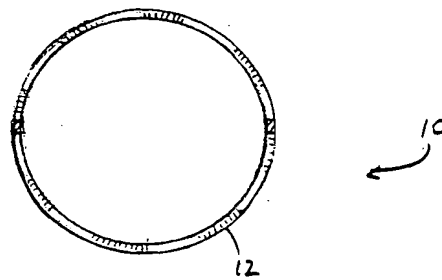


Fig. 6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/35641

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61F 13/00, 2/00; A61K 31/565; A61M 25/10, 29/00; A61P 9/10

US CL : 424/422, 423; 514/182, 824; 604/609.1, 96; 623/1.42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/422, 423; 514/182

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WEST, USPATFULL, JPO, EPO, DERWENT

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ----	US 5,866,561 A (UNGS) 02 FEBRUARY 1999, abstract; col. 2, lines 16-46; and claim 7.	1-6, 10-18, 22-25 -----
Y		7-9, 19-21
Y	US 5,962,475 A (SCHMID et al) 05 OCTOBER 1999, abstract; col. 2, lines 51-52.	7-8, 19-20
X ----	US 5,242,397 A (BARATH et al) 07 SEPTEMBER 1993, col. 1, lines 14-21; and col. 5, lines 2-4 .	9, 21 -----
Y		7-8, 19-20

☐

Further documents are listed in the continuation of Box C.

☐

See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

08 MARCH 2001

Date of mailing of the international search report

11 APR 2001

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

HELEN NGUYEN

Telephone No. (703) 308-1235